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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicants:	Thomas C. Terwilliger	Docket No.:	S-91,732
Serial No.:	09/512,962	Examiner:	A. Marschel
Filed :	February 25, 2000	Art Unit:	1631

For : LIKELIHOOD-BASED MODIFICATION OF EXPERIMENTAL CRYSTAL STRUCTURE ELECTRON DENSITY MAPS

RESPONSE TO NOTIFICATION OF NON-COMPLIANCE WITH 37 CFR 92(c)

The Examiner has issued on August 25, 2004 a notice of non-compliance with 37 CFR 192(c) for the appeal brief filed June 4, 2004. The Examiner has required that the appeal brief contain a reference to U.S. Patent Application S.N. 10/017,643 as a related case and that the Summary of the Invention set out a reference in the specification and figures applicable to each limitation in the claims on appeal.

CERTIFICATE OF MAILING/TRANSMISSION (37 CFR 1.8(a))

I hereby certify that this correspondence is, on the date shown below, being:

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Date Sept. 13, 2004

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Signature

Ray G. Wilson
(type or print name of person certifying)

Without concurring that the Examiner's requirements comply with MPEP 1206, applicant has amended the appeal brief to include the copending application as a related case and has replaced the concise summary of the invention with a table containing a listing of the claims on appeal with supporting references to the specification and figures in this case in order to meet the Examiner's requirements.

The amended appeal brief is submitted herewith in triplicate.

Respectfully submitted,

Date: 9-13-04

Signature of Attorney

Reg. No. 28,351
Phone (505) 665-3112

Ray G. Wilson
Los Alamos National Laboratory
LC/IP, MS A187
Los Alamos, New Mexico 87545

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Mail Stop Appeal Brief - Patents
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APPEAL BRIEF

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STATEMENT OF THE REAL PARTY IN INTEREST

The Regents of the University of California is the assignee of all right, title, and interest in U.S. Patent Application Serial No. 09/512,962 from the Government of the United States, United States Department of Energy.

RELATED APPEALS AND INTERFERENCES

There is an appeal pending in U.S. Patent Application S.N. 10/017,643, which is a continuation -in-part of the present case.

STATUS OF ALL CLAIMS

Claims 10-14 are pending in this case. Claims 10-14 stand rejected under 35 U.S.C. §101 as being directed to non-statutory subject matter.

STATUS OF AMENDMENTS

There are no outstanding amendments in this case.

SUMMARY OF THE INVENTION

The following table presents a comparison of the claims with the corresponding references to the specification and Figures that support the limitations.

Claim Limitation	Support location
10. A method for improving an electron density map of an experimental crystal structure, comprising the steps of:	p. 4, l. 16-17
(a) forming a model electron density map from known crystallographic information of an exemplary model crystal structure;	Fig. 1, step 12; p. 17, l. 8-10; Fig1, step 10; p. 15, l. 1-14
(b) forming model histograms of model electron densities in identified protein and solvent regions of the model electron density map;	Fig. 1, steps 14-16; p. 17, l. 10-13
(c) fitting a model probability distribution function defined by $$p(\rho_T) = \sum_k w_k \exp\left\{-\frac{(\rho - c_k)^2}{2\sigma_k^2}\right\}$$ to the model histograms, where k is separately indexed over the protein and solvent regions of the model map, $p(\rho_T)$ is a probability of an electron density at a point, w_k is a normalization factor, ρ is electron density, c_k is a mean value of ρ, and σ_k is a variance of ρ, where the fitting determines the coefficients w_k, c_k, and σ_k;	Fig. 1, steps 18-22; p. 17, l. 13-17; p. 14, l. 12-20; p. 15, l. 15-25

(d) determining a set of experimental structure factors from x-ray diffraction data for the experimental crystal structure and forming an experimental electron density map;	p. 16, l. 24-26;p. 17, l. 1-16
(e) forming separate experimental histograms of experimental electron densities over protein and solvent regions of the model electron density map:	p. 16, l. 6-17
(f) fitting an experimental probability distribution function defined by $$p(\rho_T) = \sum_k w_k \exp\left\{-\frac{(\rho - \beta c_k)^2}{2\left(\beta\sigma_k^2 + \sigma_{map}^2\right)}\right\}$$ to separate protein and solvent regions of the experimental histograms, where β is an expectation that an experimental value of ρ is less than a true value and σ_{map} is a variance, where the fitting determines the coefficients β and σ_{map};	p. 15, l. 16-29; p. 16, l. 1-5; p. 16, l. 6-19; p. 13, l. 28-29
(g) determine the overall experimental log-likelihood of the electron density in the protein and solvent regions of the experimental map from the experimental probability distribution function $$LL(\rho(\mathbf{x},\{\mathbf{F_h}\})) = \ln\begin{bmatrix} p(\rho(\mathbf{x})\|PROT)\, p_{PROT}(\mathbf{x}) \\ +p(\rho(\mathbf{x})\|SOLV)\, p_{SOLV}(\mathbf{x}) \end{bmatrix}$$ where $p_{PROT}(\mathbf{x})$ is the probability that **x** is in the protein region and $p(\rho(\mathbf{x})\|PROT)$ is the	P. 12, l. 2-7; p. 19, l. 1-6

conditional probability for $\rho(\mathbf{x})$ given that $\mathbf{x}$ is in the protein region, and $p_{SOLV}(\mathbf{x})$ and $p(\rho(\mathbf{x})\|SOLV)$ are the corresponding quantities for the solvent region;.	
(h) determine how the experimental log-likelihood of the electron density of the protein and solvent regions of the structure factor experimental electron density map would change as each experimental structure factor changes to output a revised log-likelihood of any value of each experimental structure factor;	Fig. 2, steps 36-42; p. 19, l. 8-14; p. 10, l. 111-18
(i) forming from the revised log-likelihood of experimental structure factor values a new set of structure factors; and	p. 19, l. 15-22
(j) forming a revised experimental electron density map from the revised structure factors.	p. 19, l. 20-22
11. The method according to Claim 10, wherein step (a) further includes a step of selecting the model crystal structure to be similar in size, data resolution, and atomic displacement factors to the experimental crystal structure.	p. 15, l. 6-8
12. The method according to Claim 10, wherein step (b) further includes a step of identifying protein and solvent regions by designating all points within a selected distance of an atom as "protein" and all other points as "solvent."	p. 15, l. 15-18

13. The method according to Claim 11, wherein step (b) further includes a step of identifying protein and solvent regions by designating all points within a selected distance of an atom as "protein" and all other points as "solvent."	p. 15, l. 15-18
14. The method according to Claim 10, wherein step (h) includes steps of forming a Taylor's series expansion of the log-likelihood of the experimental electron density map and evaluating terms of the Taylor's series expansion using a Fast Fourier Transform.	p. 8, l. 5-13; p. 9, l. 1-8

ISSUE PRESENTED FOR REVIEW

Do the methods recited in Claims 10-14 recite statutory subject matter under 35 U.S.C. §101 and entitled to a patent?

GROUPING OF THE CLAIMS

Applicants do not believe that any special grouping of the claims leads to a better understanding of the issues.

ARGUMENT

Appellant respectfully traverses the rejection of the claims under 35 U.S.C. §101 as directed to non-statutory subject matter. The Examiner has rejected Claims 10-14 under 35 U.S.C. §101, remarking that the claimed process is directed to non-statutory subject matter since "no physical transformation is controlled by the claim algorithm,"

which "only manipulates an electron density map which is reasonably data and not a physical material." As noted in MPEP 2106.IV.B.2.(b).(i), a process is clearly statutory "if it requires physical acts to be performed outside the computer . . . . But, "[i]f a claim does not clearly fall into one or both of the safe harbors, the claim may still be statutory if it is limited to a practical application in the technological arts."

> The notion of "physical transformation" can be misunderstood. In the first place, it is not an invariable requirement, but merely one example of how a mathematical algorithm may bring about a useful application.
> ***AT&T Corp. v. Excel Communications, Inc.***, 172 F.3d 1352, 50 USPQ 2d 1447, 1454 (Fed. Cir. 1999), *cert denied*, 120 S. Ct. 368 (1999), *on remand*, 52 USPQ2d 1865 (D. Del. 1999)
>
> Today, we hold that the transformation of data, representing discrete dollar amounts, by a machine through a series of mathematical calculations into a final share price, constitutes a practical application of a mathematical algorithm, formula, or calculation, because it produces "a useful, concrete and tangible result"--a final share price momentarily fixed for recording and reporting purposes and even accepted and relied upon by regulatory authorities and in subsequent trades.
> ***State Street Bank & Trust Co. v. Signature Fin. Group, Inc.***, 47 USPQ 2d 1596, 1601 (Fed. Cir.), ***cert. denied***, 525 U.S. 1093 (1999)
>
> It is clear from the written description of the . . . patent that AT&T is only claiming a process that uses the Boolean principle in order to determine the value of the PIC indicator. The PIC indicator represents information about the call recipient's PIC, a useful, non-abstract result that facilitates differential billing of long-distance calls made by an IXC's subscriber. Because the claimed process applies the Boolean principle to produce a use, concrete, tangible result without pre-empting other uses of the mathematical principle on its face the claims process comfortably falls within the scope of Section 101. *See Arrhythimia Research Tech. Inc. v. Corazonix Corp.*, 958 R.2d 1053, 1060, 22 USPQ2d 1033, 1039 (Fed. Cir. 1992) ('That the product is numerical is not a criterion of whether the claim is directed to statutory subject.') *Id.*.
> ***AT&T Corp. v. Excel Communications, Inc.***, *supra.* at 1452.

Appellant's claimed method is the application of mathematical algorithms to modify "an electron density map of an experimental crystal structure," resulting in a new electron density map, as recited in Claim 10. There is no longer in the law any requirement that the method result in any "physical transformation" as would be required by the Examiner. Further, the application of the recited mathematical manipulations is clearly directed to a specified application, the formation of a revised

electron density map of a crystal structure from a starting electron density map. There is no attempt to claim or forestall the use of any mathematical manipulation in any other application. See, e.g., the following claim steps:

(a) forming a model electron density map from known crystallographic information of an exemplary model crystal structure;

(b) forming model histograms of model electron densities in identified protein and solvent regions of the model electron density map;

(c) fitting a model probability distribution function . . .to the model histograms . . .;

(d) determining a set of experimental structure factors from x-ray diffraction data for the experimental crystal structure and forming an experimental electron density map;

(g) forming from the revised log-likelihood of experimental structure factor values a new set of structure factors;

(j) forming a revised experimental electron density map from the revised structure factors.

Independent Claim 10 and dependent Claims 11-14 clearly produce a concrete, tangible result within the teachings of AT&T Corp., *supra.,* and State Street Bank & Trust Co., supra. Even assuming that the electron density map is "reasonably data and not a physical material," as characterized by the Examiner, this is not a criteria for determining whether the claims are directed to statutory subject matter.

CONCLUSION

Claims 10-14 recite a method that is a "practical application in the technological arts" producing a useful result and constitute statutory subject matter under 35 U.S.C. §101. The rejection of Claims 10-14 as being directed to nonstatutory subject matter should be withdrawn.

Respectfully submitted,

Date: 9-13-04

Signature of Attorney

Reg. No. 28,351
Phone (505) 665-3112

Ray G. Wilson
Los Alamos National Laboratory
LC/IP, MS A187
Los Alamos, New Mexico 87545

APPENDIX A - CLAIMS ON APPEAL

10. A method for improving an electron density map of an experimental crystal structure, comprising the steps of:

(a) forming a model electron density map from known crystallographic information of an exemplary model crystal structure;

(b) forming model histograms of model electron densities in identified protein and solvent regions of the model electron density map;

(c) fitting a model probability distribution function defined by

$$p(\rho_T) = \sum_k w_k \exp\left\{-\frac{(\rho - c_k)^2}{2\sigma_k^2}\right\}$$

to the model histograms, where k is separately indexed over the protein and solvent regions of the model map, $p(\rho_T)$ is a probability of an electron density at a point, w_k is a normalization factor, ρ is electron density, c_k is a mean value of ρ, and σ_k is a variance of ρ, where the fitting determines the coefficients w_k, c_k, and σ_k;

(d) determining a set of experimental structure factors from x-ray diffraction data for the experimental crystal structure and forming an experimental electron density map;

(e) forming separate experimental histograms of experimental electron densities over protein and solvent regions of the model electron density map;

(f) fitting an experimental probability distribution function defined by

$$p(\rho_T) = \sum_k w_k \exp\left\{-\frac{(\rho - \beta c_k)^2}{2\left(\beta\sigma_k^2 + \sigma_{map}^2\right)}\right\}$$

to separate protein and solvent regions of the experimental histograms, where β is an expectation that an experimental value of ρ is less than a true value and σ_{map} is a variance, where the fitting determines the coefficients β and σ_{map};

(g) determine the overall experimental log-likelihood of the electron density in the protein and solvent regions of the experimental map from the experimental probability distribution function

$$LL\left(\rho(\mathbf{x},\{\mathbf{F_h}\})\right) = \ln\left[p\left(\rho(\mathbf{x})|PROT\right)p_{PROT}(\mathbf{x}) + p\left(\rho(\mathbf{x})|SOLV\right)p_{SOLV}(\mathbf{x})\right]$$

where $p_{PROT}(\mathbf{x})$ is the probability that **x** is in the protein region and $p\left(\rho(\mathbf{x})|PROT\right)$ is the conditional probability for $\rho(\mathbf{x})$ given that $\mathbf{x}$ is in the protein region, and $p_{SOLV}(\mathbf{x})$ and $p\left(\rho(\mathbf{x})|SOLV\right)$ are the corresponding quantities for the solvent region;

(h) determine how the experimental log-likelihood of the electron density of the protein and solvent regions of the structure factor experimental electron density map would change as each experimental structure factor changes to output a revised log-likelihood of any value of each experimental structure factor;

(i) forming from the revised log-likelihood of experimental structure factor values a new set of structure factors; and

(j) forming a revised experimental electron density map from the revised structure factors.

11. The method according to Claim 10, wherein step (a) further includes a step of selecting the model crystal structure to be similar in size, data resolution, and atomic displacement factors to the experimental crystal structure.

12. The method according to Claim 10, wherein step (b) further includes a step of identifying protein and solvent regions by designating all points within a selected distance of an atom as "protein" and all other points as "solvent."

13. The method according to Claim 11, wherein step (b) further includes a step of identifying protein and solvent regions by designating all points within a selected distance of an atom as "protein" and all other points as "solvent."

14. The method according to Claim 10, wherein step (h) includes steps of forming a Taylor's series expansion of the log-likelihood of the experimental electron density map and evaluating terms of the Taylor's series expansion using a Fast Fourier Transform.